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Palladium-Assisted Regioselective C−H Cyanation of Heteroarenes Using Isonitrile as Cyanide Source

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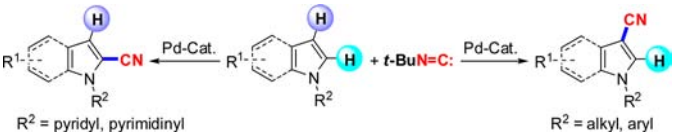
ABSTRACT



A palladium-catalyzed regioselective C−H cyanation of heteroarenes was achieved using *tert*-butyl isocyanide as "CN" source, which provides a new and unique strategy for the preparation of (hetero)aryl nitriles. Indoles, pyrroles, and aromatic rings could be efficiently cyanated through C−H bond activation with high regioselectivity.

The nitrile unit is exemplified as a unique structural motif in many marketing drugs used to treat cancer and depression diseases such as Arimidex, Casodex, Cipralex, Femara and Lexapro. In addition, the nitrile moiety has also served as a versatile building block and effective precursor for various functional group transformations leading to the formation of aldehydes, amides, amidines, amines, carboxyl derivatives and heterocycles.[1] The prevalence of this physiologically important unit, found in therapeutic agents as well as in natural products,[2] has prompted the development of many useful methods for their preparation (Scheme 1).[3] Among these methods, the Sandmeyer[4] and Rosenmund−von Braun[5] reactions represent two classical methods for the preparation of organonitriles. A metal-catalyzed cyanation reaction was normally achieved by coupling reactions of aryl (pseudo)halides with a range of cyanating reagents.[3] Oxidative cyanation through C−H bond activation could be demonstrated by using metal cyanides,[6a−e] CH_3NO_2,[6f] NCTS,[6g] TMSCN,[6h] TsCN,[6i] BrCN,[6j] Me_3SiN_3[6k] and acetone cyanohydrin[6l] as "CN" sources. All these methods are, however, either impracticable by using notorious toxic cyanide sources, or incompatible with sensitive functionalities because of the harsh conditions required during these transformations, or generate stoichiometric amounts of metal wastes during

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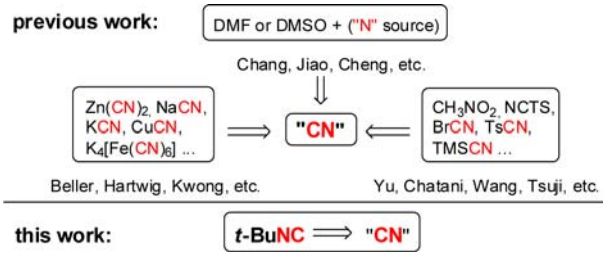
the reaction. An elegant new protocol of generating a "CN" unit was developed by Chang and his co-workers using DMF and ammonia[7a] or ammonium iodide[7b] as "CN" source via palladium-catalyzed or copper-mediated reactions. Recently, Jiao et al. demonstrated a novel Pd- catalyzed direct cyanation of indoles and benzofurans through C−H functionalization employing DMF as both reagent and solvent.[8] Alternatively, DMSO could also be applied in the cyanation reaction instead of DMF.[9]

Scheme 1. Different Sources of "CN" in Cyanation Reactions

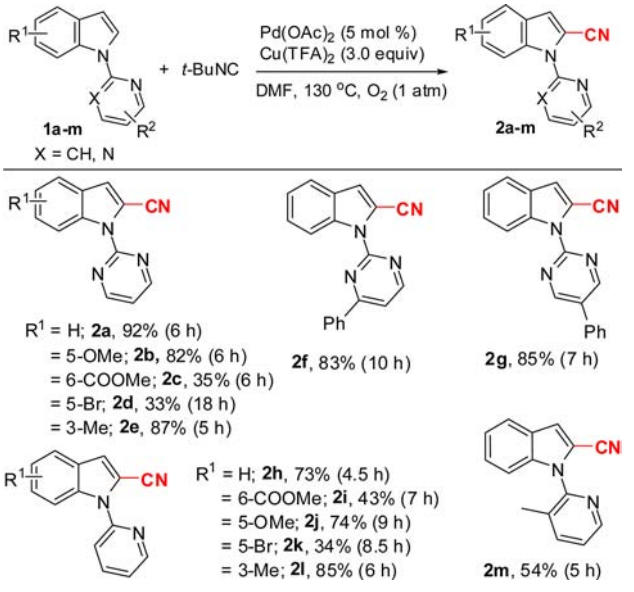


Isonitriles are uniquely versatile intermediates in organic synthesis because of their structural and reactive properties and have proven themselves to be powerful C1 building blocks toward a variety of desirable molecules.[10] Sustainability contribution of isonitriles has been widely recognized in the multicomponent Passerini and Ugi reactions.[10c,11] Recently, several examples have been reported via metal-catalyzed intermolecular isonitrile insertion reaction by means of C−H bond activation.[12] However, employing readily available isonitrile as a successful source of "CN" unit has not yet been disclosed. Herein, we report a novel palladium-catalyzed regioselective cyanation of heteroarenes through C−H bond functionalization using *tert*-butyl isocyanide as "CN" source (Scheme 1). To our knowledge, this approach represents the first example for highly regioselective C−H cyanation using isonitrile as crucial "CN" source.

To determine the feasibility of chelation effect of a pyrimidyl group in the C−H bond cyanation reaction,[13] we initially examined the reaction by exploring *N*-(2-pyrimidyl)indole[14] (**1a**) with *tert*-butyl isocyanide in the presence of $Pd(OAc)_2$ (5 mol %) in toluene using $Cu(OAc)_2$ as oxidant. Intriguingly, the 2-cyano substituted indole **2a** was produced in 12% yield after reacting for 24 h at 120 °C under air (entry 1, Table S1; see the Supporting Information). An extensive screening concerning solvents, copper resources, atmosphere and temperature revealed that the use of $Cu(TFA)_2$ as oxidant in DMF at 130 °C under atmospheric oxygen turned out to be the best choice and resulted in 92% yield. Decreased yield could be afforded without using palladium catalyst (entry 13), and trace amount of 2-cyanoindole product was detected in the absence of $Cu(TFA)_2$ (entry 14) or *t*-BuNC (entry 15), which indicated that both the Cu(II) and isocyanide were crucial to proceed this cyanation reaction.

With the optimized reaction conditions in hand, we then extended the reaction with a range of substrates. As illustrated in Scheme 2, this reaction was compatible with functionalized *N*-pyrimidyl substituted indoles bearing substitutions at C3-, C5- or C6-position (**2b**−**2e**, Scheme 2), and afforded 2-cyanoindoles in good to excellent yields with high regioselectivity. *N*-Pyrimidyl indoles containing both electron-donating (**2b** and **2e**) and electron-withdrawing groups (**2c** and **2d**) afforded 2-cyanated products predominately. Indoles with electron-donating groups usually gave better yields than those with electron-withdrawing groups. For substrate having a bromo substitution, the yield turned out to be lower (**2d**), the reason may be due to the competitive reactions at the reactive bromine. For those substrates with phenyl group substituted at pyrimidine ring, 2-cyanoindoles could be furnished in good yields (**2f** and **2g**). It should be noted that 1-(4-phenylpyrimidin-2-yl)-1*H*-indole (**1f**), which has two potential cyanation positions, gave exclusive product

Scheme 2. 2-Cyanation of Substituted Indoles[a,b]



[a] Reaction conditions: **1a**−**m** (0.3 mmol), *t*-BuNC (3.0 equiv), $Pd(OAc)_2$ (5 mol %), $Cu(TFA)_2$ (3.0 equiv), DMF (1.5 mL) under O_2 balloon at 130 °C. [b] Isolated yield.

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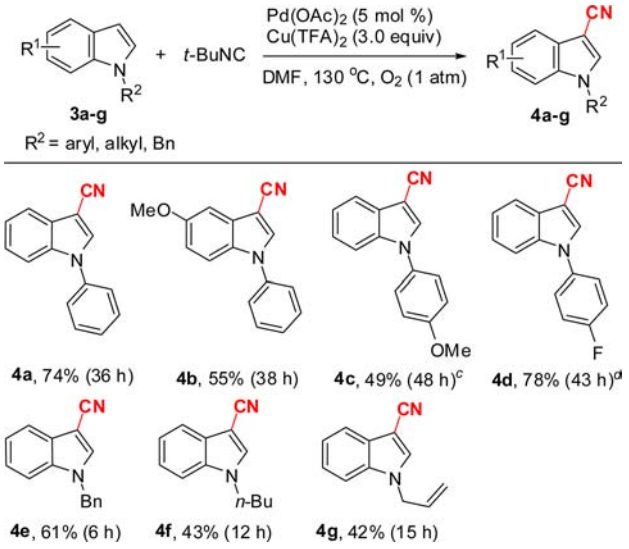
2f in 83% yield. The given result indicated that the C2-position of indole is more easily cyanated compared with the *ortho* sp^2 C−H bond of phenyl ring attached at 4-position of pyrimidine. Furthermore, this cyanation reaction could also proceed well for *N*-pyridyl indoles (**2h**−**2m**). The identity of **2j** was determined by spectra analysis and further confirmed by X-ray crystallographic analysis.[15]

Encouraged by the success of a direct C−H cyanation reaction of *N*-pyrimidyl indoles, to further explore the generality and scope of this practical approach, a variety of *N*-alkyl or *N*-aryl substituted indoles were investigated (Scheme 3). To our surprise, this reaction predominantly took place on the C3-position of indole ring in moderate to good yields, which is different from those with *N*-pyrimidyl or pyridyl substitutions. No regioisomeric products could be isolated or detected by LC−MS and proton NMR. The *N*-alkyl substrates (**4e**−**4g**) normally proceeded faster than *N*-aryl indoles (**4a**−**4d**). In addition, for substrate with allyl group (**4g**), the C=C double bond remained intact under optimized conditions.

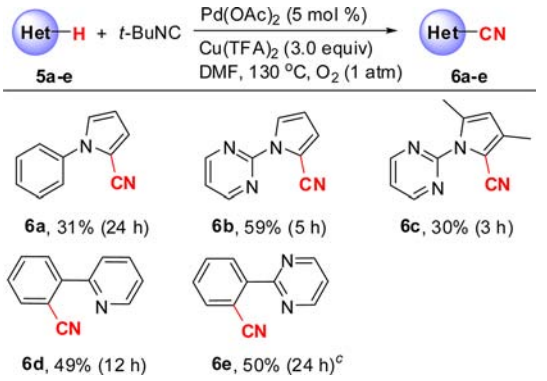
Scheme 3. 3-Cyanation of Substituted Indoles[a,b]



[a] Reaction conditions: **3a**−**g** (0.3 mmol), *t*-BuNC (3.0 equiv), Pd(OAc)$_2$ (5 mol %), Cu(TFA)$_2$ (3.0 equiv), DMF (1.5 mL) under O_2 balloon at 130 °C. [b] Isolated yield. [c] The yield based on 73% conversion of **3c**. [d] At 140 °C, the yield based on 81% conversion of **3d**.

This newly established protocol was not limited to indoles. *N*-Substituted pyrroles were also found to be suitable substrates for this regioselective cyanation under the same reaction conditions (Scheme 4). For instance, *N*-phenyl and *N*-pyrimidyl pyrroles were efficiently converted to desired cyanated products **6a** and **6b**, respectively. In this regard, both phenyl and pyrimidyl substituted pyrroles could be cyanated selectively at the C2-position of the pyrrole ring. When extending to multisubstituted pyrrole, 2-cyanated pyrrole could be identified regioselectively in moderate yield (**6c**). To our delight, when attempting to explore the cyanation reaction for arylpyridine and arylpyrimidine substrates, regioselective *ortho*-C−H cyanation occurred in the aromatic ring and afforded the cyano product in moderate yields (**6d** and **6e**).

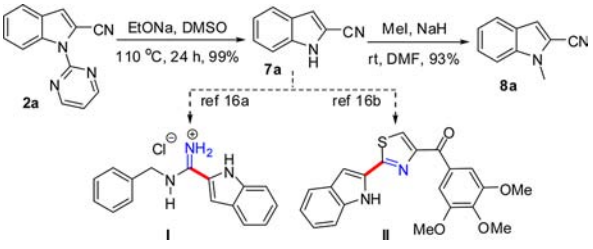
Scheme 4. Regioselective Cyanation of Heteroarenes[a,b]



[a] Reaction conditions: **5a**−**e** (0.3 mmol), *t*-BuNC (3.0 equiv), Pd(OAc)$_2$ (5 mol %), Cu(TFA)$_2$ (3.0 equiv), DMF (1.5 mL) under O_2 balloon at 130 °C. [b] Isolated yield. [c] *N*-Methyl pyrrolidone (1.5 mL) was used; the yield based on 54% conversion of **5e**.

The produced *N*-pyrimidyl 2-cyanoindoles are versatile synthetic intermediates with easily removable pyrimidinyl group. For example, free (NH)-indole **7a**[16] could be prepared in nearly quantitative yield from **2a**, which gave corresponding 2-cyano-*N*-methylindole **8a** in 93% yield (Scheme 5). This method provided a successful extension and complement for synthesis of *N*-alkyl 2-cyanoindoles. The generated **7a** has been widely applied to synthetic pharmaceutical agents with a broad range of bioactivities. Following a literature method, a novel NR2B selective NMDA receptor antagonist **I**[16a] could be easily constructed from **7a**. Also, as a potent and orally bioavailable anticancer agent, **II**[16b] could be converted from **7a** using known method (Scheme 5).

Scheme 5. Synthesis of Free (NH)-Indole and Its Application



To probe the role of *t*-BuNC in this cyanation reaction, several experiments were explored under the optimized

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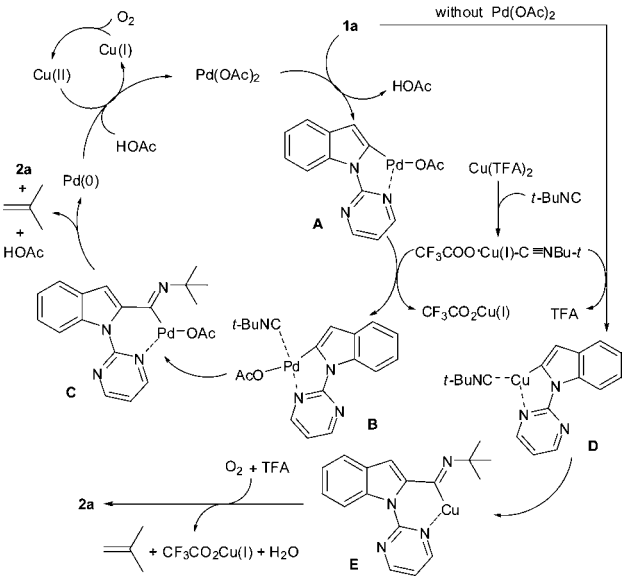
reaction conditions, including (i) when the reaction was conducted in the absence of *t*-BuNC (Table S1 (Supporting Information), entry 15) or using *tert*-butylamine instead of *t*-BuNC, only trace amount of **2a** was found from **1a**; and (ii) 57% yield of **2a** could be achieved when the solvent was switched to toluene from DMF. These results indicated that this cyanation reaction was not followed the Chang[7] and Jiao's procedure[8] and the generated cyano group was derived from *t*-BuNC.

To define the possible intermediates and pathway, the following control experiments were performed. When the indole substrates **1a** and **3a** were performed under optimized reaction conditions in the absence of $Pd(OAc)_2$, the yield was decreased to 80 and 41%, respectively. Evidently, the palladium catalyst played an important role to promote the cyanation reaction. We attempted the reaction of **1a** with *tert*-butyl cyanide under the standard reaction conditions, and only trace amount of **2a** was observed, which suggested that during the conversion of *t*-BuNC into a "CN" unit, the reaction might not go through the *tert*-butyl cyanide intermediate.[17] When CuCN was used instead of *t*-BuNC and $Cu(TFA)_2$ during the reaction, the cyanated indole **2a** was afforded in only 13% yield, and this result implied that the reaction did not mainly proceed via the CuCN intermediate, which may be generated from *t*-BuNC and $Cu(TFA)_2$. However, when a Cu(I) carboxylate-isonitrile complex [$CF_3COO\cdot$Cu(I)-CNBu-*t*][18] was used instead of *t*-BuNC and $Cu(TFA)_2$, **2a** could be achieved in 97% yield after reacted for 6 h, which indicated that this complex might be the key intermediate during the reaction.

On the basis of these results, we proposed the plausible mechanism for the formation of cyanated indole (Scheme 6). This reaction may involve the formation of C−Pd bond in the first step to give intermediate **A**. The formed intermediate **A** presumably reacts with Cu(I) carboxylate-isonitrile complex to afford intermediate **B**, followed by the migratory insertion of isocyanide to generate intermediate **C**.[19] Subsequent *β*-*tert*-butyl elimination of intermediate **C** gives the product **2a** together with concomitant expulsion of isobutene,[20] and the palladium catalyst could be regenerated by the oxidation of Cu(II) and atmospheric oxygen. In the absence of palladium, the reaction will go through intermediates **D** and **E** followed by reductive elimination of Cu(I) to give product **2a**. For *N*-alkyl or *N*-aryl substituted

Scheme 6. Plausible Mechanism for Synthesis of **2a** from **1a**



indoles **3**, direct electrophilic palladation will occur at 3-position to give corresponding C3-palladated intermediate, which will lead to 3-cyanated indoles.

In summary, we have developed a novel palladium-catalyzed regioselective cyanation of heteroarenes through C−H bond functionalization by using *tert*-butyl isocyanide as a new "CN" source. This approach offers a unique strategy and alternative route for preparation of (hetero)aryl nitriles in good to excellent yields with high regioselectivity. The nature of the *N*-substitution is crucial in controlling the regioselectivity of the reaction, and as a result, the cyanation can be directed to either the C-2 or C-3 position of indoles. Further insight into the mechanism, reaction scope, and the synthetic applications for bioactive compounds are under investigation.

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Supporting Information Available. Table S1, experimental procedures and characterization data for all compounds, and X-ray structure of **2j** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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